Alberta Heritage Foundation
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Hyperbaric oxygen therapy – recent findings on evidence for its effectiveness

David Hailey

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This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion, and attempts to be current to the date of publication. Comments received following circulation of the draft have been considered in preparation of the current version which has been issued as an interim report, pending further external review.

Additional information and comments relative to the paper are welcome, and should be sent to:

Director, Health Technology Assessment
Alberta Heritage Foundation for Medical Research
1500, 10104 -103 Avenue
Edmonton
Alberta T5J 4A7
CANADA

Tel: 780-423-5727, Fax: 780-429-3509

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INTRODUCTION

This paper has been prepared following interest by the College of Physicians & Surgeons of Alberta in obtaining advice on recent information on evidence of the effectiveness of hyperbaric oxygen therapy (HBOT). Of particular interest was HBOT of non-healing peripheral skin ulcers and the use of transcutaneous oxygen (TCO) measurement as a test prior to commencing treatment. Another area of interest was the use of HBOT in the management of carbon monoxide (CO) poisoning.

The paper is intended to provide an indication of opinions on the effectiveness or efficacy of HBOT applications reached in recent health technology assessments and systematic reviews and of selected findings reported in the literature. No detailed review of this material has been undertaken and reference to the original publications should be made for further information and consideration of the summaries provided here. Economic and cost information has not been considered.

HBOT has been used in health care for many decades and is well established in Alberta. In 1998, AHFMR completed a health technology assessment of HBOT which included a summary of evidence on its effectiveness [1,2]. HBOT has been applied to many clinical situations but in the AHFMR assessment, review of effectiveness was limited to its use in twelve applications that appeared to be most widespread. Appraisal was primarily based on material identified through electronic data bases to late 1997. The assessment concluded that:

- HBOT was established as the standard of care for decompression sickness and gas embolism.
- There was evidence that HBOT provided benefit in severe carbon monoxide poisoning, osteoradionecrosis – mandible, diabetic leg ulcers and gas gangrene.
- There was insufficient evidence to support the routine use of HBOT for soft tissue radiation injuries or necrotizing soft tissue infections.
- Available evidence did not support the use of HBOT for refractory osteomyelitis, thermal burns, compromised skin grafts/ flaps, exceptional blood loss anaemia or ischemic traumatic peripheral injuries.

In some of the indications for which there was evidence of efficacy or effectiveness, further qualification of possible benefits from HBOT was needed because of the need for rapid referral following occurrence of the condition to treated.

In the present review, further evidence has been considered for these twelve conditions and other potentially significant applications of HBOT, drawing on recent health technology assessments from other agencies and selected publications that have appeared in the medical literature.

METHODS

Searches were undertaken of the PubMed, EMBASE and HTA data bases from 1998 to 2003, using the search terms hyperbaric oxygen treatment, hyperbaric oxygen therapy, transcutaneous oxygen measurement and transcutaneous oxygen tension.

Note was taken of the findings of the health technology assessments and systematic reviews located. In addition, summaries of selected studies that have been reported in the literature were noted.

Recent Conclusions on HBOT Applications

Safety

The AHFMR assessment listed contraindications and complications associated with HBOT and concluded that it was regarded as a safe treatment from which few patients had serious side effects.

Potential risks for patients undergoing HBOT are discussed in the Australian report by MSAC [3]. It notes that most adverse events are self-limiting and resolve after termination of therapy. Serious, life-threatening events are rare. Also, published guidelines seek to provide industry-wide acceptance of recommendations and requirements for the safe operation of hyperbaric facilities. Serious adverse events associated with HBOT that were reported in some studies on wound healing are referred to by Wang et al. [4]

Decompression sickness, air and gas embolism.

Assessments by MSAC in Australia [3] and AETMIS in Québec [5] accept the position that HBOT is widely accepted as standard clinical care in the management of these conditions for which there are limited alternative treatment options.

Gas gangrene

Effectiveness of HBOT for treatment of gas gangrene was also accepted in assessments from AETMIS, MSAC and the US Agency for Healthcare Research and Quality (AHRQ) [3,5,6].

Carbon monoxide poisoning

Opinion on this application has been shifted by the recent RCT of Weaver at al. [7] which showed long term benefits from use of HBOT. Findings of systematic reviews and the assessments from the Wessex Institute (STEER) [8] and MSAC [3] were generally negative. The STEER findings have now been modified and are more positive, though with some cautions. The AETMIS report supports use of HBOT in this application [5]. Details of reports are shown in the table.

While the study by Weaver et al. provides important evidence, the effectiveness of HBOT in this application is likely to depend on a number of factors, as suggested by the STEER report, which will need to be carefully considered by operators and those who refer persons with CO poisoning for treatment.

Table 1: Publications on CO poisoning

Source	Summary of evidence	Conclusions
Dent THS, 2002 [8] HTA report, STEER	One systematic review found three trials of adequate quality on the effectiveness of HBOT in the treatment of CO poisoning, including a total of 455 people. It concluded that there is no evidence that hyperbaric oxygen reduces the frequency of neurological symptoms at one month, compared with normobaric oxygen.	Found no reliable evidence that was not considered by the review, no evidence for longer term effects, and no evidence that people should be selected for HBOT according to the severity of CO poisoning. Opinion modified by results of study by Weaver et al. – "now conclude that it is likely that repeated sessions of hyperbaric oxygen at three atmospheres reduces neuropsychological sequelae in the short and long term compared with one session of normobaric oxygen therapy in people with CO poisoning. However, results of previous studies suggest the magnitude of benefit may be highly sensitive to the pressure at which oxygen is delivered, the number of sessions of treatment and the oxygen content of control treatments."
Weaver et al., 2002 [7] RCT	HBOT reduced incidence of cognitive sequelae at 6 weeks compared with normobaric therapy in people with CO poisoning (AR: 25% *v* 46%, OR 0.39, 95% CI 0.20to 0.78, P=0.007). Results similar after adjustment for baseline differences in cerebellar dysfunction. Similar results at 12 mo follow up (AR 18% *v* 33%, OR 0.37, 95% CI 0.19 to 0.73, P=0.004).	Three hyperbaric-oxygen treatments within a 24-hour period appeared to reduce the risk of cognitive sequelae 6 weeks and 12 months after acute CO poisoning.
MSAC, 2000 [3] HTA	Used review of Juurlink et al.	Insufficient evidence to support public funding
Juurlink et al., 2003 [9] Systematic review	Six RCTs identified, three included in primary analysis	No evidence that unselected use of HBOT of acute CO poisoning reduces frequency of neurological symptoms at one mo. Evidence from available RCTs insufficient to provide clear guidelines for practice.

Table 1: Publications on CO poisoning (cont'd)

Source	Summary of evidence	Conclusions
Saunders P, 2000 [10] Systematic review	One double blind study reported a negative effect of HBOT, two studies, one double blind and one non-blind, reported no effect. Three studies, two of which were non-blind, reported a positive effect.	Overall the best quality studies found no effect. No convincing evidence that it is of benefit for the treatment of CO poisoning (severe or moderate),
AETMIS, 2000 [5] HTA	[Recommendations in summary]	HBOT recommended for treatment of CO poisoning
Hampson & Zmaeff, 2001 [11] Case series	18 patients were treated with HBOT after resuscitation from CO-associated cardiac arrest, ave 4.3h after poisoning. All patients died. Medical directors of HBOT facilities estimated a 74% likelihood of survival for a hypothetical patient with this presentation.	Survey results suggest that physician education regarding this subset of CO -poisoned patients is needed. The prognosis of this condition should be considered when making triage and treatment decisions for patients poisoned to this severity
Chou KJ et al., 2000 [12] Review of medical records	150 children with CO poisoning over 3y period who were treated with HBOT	Children with CO poisoning alone who are treated with HBOT are at low risk for dying regardless of initial COHb level. Children with CO/ smoke inhalation have a significantly higher risk of dying than those children with COP alone [22.6% vs. 0%,]. A combination of smoke inhalation, low temperature, high COHb level, respiratory arrest, and cardiac arrest is highly associated with death.
Hawkins M, 2000 [13] Comparison of case series with other study	16.1% hospital mortality and 3.8% severe short-term memory loss, compared with 30% hospital mortality and 20% incidence of serious neurological deficit after treatment with normobaric oxygen; outcome was poor in 19.4% and 44.3% of those treated with hyperbaric and normobaric oxygen, respectively ($P < 0.05$).	

Osteoradionecrosis

Health technology assessments seem generally supportive of this application, while noting the limited evidence of benefit that is available and the need for further studies (see Table 2).

Table 2: HBOT and osteradionecrosis

Source	Summary of evidence	Conclusions
Patterson J, 2002 [14] HTA (STEER)	Two RCTS of people who had received radiotherapy to the mouth considered in a systematic review	Both RCTs had important methodological weaknesses, limited evidence that HBOT may help to prevent mandibular osteoradionecrosis following oral radiotherapy. Found no reliable evidence on HBOT effects in people with or at high risk of non-mandibular osteoradionecrosis.
MSAC, 2000 [3]	One RCT, one comparative study	Serious condition in which HBOT may have a beneficial effect. Further studies are required to provide more conclusive evidence but are difficult to undertake. Public funding should be continued for HBOT use.
AETMIS, 2000 [5] HTA	[Recommendation from summary]	HBOT recommended for treatment of osteoradionecrosis
AHRQ, 2001 [6]	Considered two RCTs, one case series	There is sufficient objective evidence that HBOT aids in wound healing
Saunders P, 2000 [10] Systematic review	One study with only 12 participants reported significant improvement in healing; second larger non-blind RCT (n=74) found a significant reduction in the rate of osteoradionecrosis in the intervention group compared to penicillin treatment.	No convincing evidence that HBOT is of benefit for the treatment of osteoradionecrosis.
Maier A et al., 2000 [15] Controlled non - randomized study	Of 41 patients with osteoradionecrosis of the mandible treated by radical resection and EBRT, 20/41 received HBOT, 21/41 surgery and antibiotics alone. Overall success for HBOT in 13/20, 14/21 for other group	Do not recommend HBOT for the treatment of osteoradionecrosis.

Soft tissue radionecrosis

The MSAC assessment found there was insufficient evidence to support this application (see Table 3). The AHRQ report noted that no controlled studies had been located but that case series suggested evidence of benefit. A summary of an article based on the AHRQ assessment [4] states that results suggest that HBO may be beneficial as an adjunctive therapy for this condition.

Table 3: HBOT and soft tissue radionecrosis

Source	Summary of evidence	Conclusions
MSAC, 2000 [3] HTA	No articles met selection criteria	Insufficient evidence, public funding not supported
AHRQ, 2001 [6] HTA	No controlled studies located	Evidence from case series suggesting evidence of benefit

Diabetic wounds

Health technology assessments were generally supportive of the use of HBOT in this application, though a German assessment recommended against coverage and a systematic review was neutral.

The recent comparative study by Kalani et al. [16] in Sweden provides some evidence for long term benefits from this application.

A case series in which topical HBOT and low energy laser treatment were used gives an indication of a potential alternative option; there is no indication of the contribution made by the laser and this approach would need validation.

Table 4: HBOT and diabetic wounds

Source	Summary of evidence	Conclusions
MSAC, 2000 [3] HTA	Located two RCTs and three other comparative studies	Evidence that HBOT is effective in promoting wound healing, and reducing the length of hospital stays and the likelihood of major amputations in patients with diabetic wounds. Public funding for HBOT should be continued.
AETMIS, 2000 [5] HTA	[Recommendation from summary]	HBOT recommended for treatment

Table 4: HBOT and diabetic wounds (cont'd)

Source	Summary of evidence	Conclusions
Mason J, 1999 [17] Systematic review	Two RCTs - one trial reported ulcers in both groups improved significantly, but NSD between the groups at 2 weeks follow-up. Other reported that major amputation lower in the treated group (8.6%) than control group (33.0%) p=0.016. NSD in minor amputations. The trials had a number of differences including severity of ulcers being investigated and the type of oxygen therapy used.	The role of HBOT can neither be ruled in nor out on the basis of available evidence.
AHRQ, 2001 [6] HTA	Two RCTs, four non-randomised	There is sufficient objective evidence that HBOT aids in wound healing
Gwalick C et al. [Standing Committee of Statutory Health Insurance Physicians and Sickness Funds (Germany)], 2001 [18]	HTA – review of literature, submissions [in all considered 40 applications] For diabetic foot ulcers most trials were retrospective case series, which, in view of the established therapies, cannot be used as a sound basis for the acceptance of HBOT as a new technology. Some studies were planned as RCTs but had serious methodological flaws.	The Committee decided once again to decline coverage of HBOT in German ambulatory health care.
Kalani M et al., 2002 [16] Prospective non-randomised study	N=38 diabetic patients (30 males) with chronic foot ulcers. N=17 underwent 40-60 sessions of HBOT, n=21 treated conventionally. Follow-up time was 3 years. At 3y 76% of HBOT healed with intact skin vs 48% for controls. Amputation in 12% HBOT, 33% control	Adjunctive HBOT can be valuable for treating selected cases of hypoxic diabetic foot ulcers.
Landau Z, Schattner A, 2001 [19] Prospective case series	Topical HBOT + low energy laser as treatment N=100 consecutive patients with chronic diabetic foot ulcers refractory to 4.5 +/- 1.2 months of comprehensive treatment, conventional treatment was continued as necessary. 81% cure after 25 +/- 13 treatments over 3.2 +/- 1.7 months. On follow-up (median 18 months), only 3/81 (4 %) had reulceration.	THBO/LEL therapy may be a safe, simple, and inexpensive early adjunctive treatment for patients with chronic diabetic foot ulcers.

Necrotising soft tissue infections

Evidence of benefit remains limited. Three HTAs supported use of HBOT in this application and one considered that HBOT remains an experimental treatment.

Osteomyelitis

The MSAC report considered there was insufficient evidence for this application and recommended against public funding. The AHRQ report appears to consider HBOT as beneficial though the basis for this finding is not entirely clear.

Non – diabetic wounds

Both the MSAC and AHRQ assessments recommend against the use of HBOT.

Table 5: HBOT and soft tissue necrotising infections

Source	Summary of evidence	Conclusions
Bissett AF, 2002 [20] HTA (STEER)	Found three retrospective comparisons of case series of people with necrotising fasciitis or Fournier's gangrene who did and did not have HBOT.	No reliable evidence. Until evidence from randomised controlled trials becomes available hyperbaric oxygen remains an experimental treatment for necrotising fasciitis or Fournier's gangrene.
MSAC, 2000 [3]	Six comparative studies	Serious conditions in which HBOT may have a beneficial effect. Further studies are required to provide more conclusive evidence but are difficult to undertake. Public funding should be continued for HBOT use in these conditions.
AETMIS, 2000 [5] HTA	[Recommendation from summary]	HBOT recommended for treatment.
AHRQ, 2001 [6]	HTA – concurs with findings in other HTAs. Refers to six non randomized studies and three case series.	There is sufficient objective evidence that HBOT aids in wound healing.

Table 6: HBOT and osteomyelitis

Source	Summary of evidence	Conclusions
MSAC, 2000 [3] HTA	One comparative study, notes may not be generalisable.	Insufficient evidence, public funding not supported.
AHRQ, 2001 [6] HTA	States that concurs with findings in other HTAs. One non randomized trial, one case series.	Beneficial adjunctive therapy to wound care.

Table 7: HBOT and non-diabetic wounds

Source	Summary of evidence	Conclusions
AHRQ, 2001 [6] HTA	One case series.	More research is needed to assess efficacy of HBOT.
MSAC, 2000 [3] HTA	Only one study (RCT) met inclusion criteria.	Insufficient evidence, public funding not supporte.

Thermal burns

The MSAC report and a systematic review consider there is insufficient evidence of benefit.

Table 8: HBOT and thermal burns

Source	Summary of evidence	Conclusions
Saunders P, 2000 [10] Systematic review	A small blinded RCT (n=16) found a significant reduction in healing time in the HBOT group vs placebo. Larger non-blind RCT (n=125)found no difference in length of stay, mortality or number of surgeries. A third blinded small RCT (n=12) in healthy volunteers, found improvements in the HBOT at the start of the study but these were no longer found at the end of the study.	No convincing evidence of benefit.
MSAC, 2000 [3]	Studies were disparate in their research designs, varied in their populations, inconsistent in their therapies, and conflicting in their outcomes and conclusions.	Insufficient evidence, public funding not supported.

Crush injury

Use of HBOT was not supported by MSAC or by a systematic review.

Table 9: HBOT and crush injury

Source	Summary of evidence	Conclusions
Saunders P, 2000 [10] Systematic review	A double-blind RCT of 36 patients found a significant effect on wound healing in HBOT group.	No convincing evidence of benefit.
MSAC, 2000 [3]	Two comparative studies.	Insufficient evidence [*soft tissue injuries including acute ankle sprains and crush injuries*] public funding not supported.

Skin grafts and flaps

There continues to be only limited evidence in support of HBOT in this application. A systematic review and the MSAC report consider there is insufficient evidence, while AHRQ considers there is sufficient objective evidence.

Table 10: HBOT and compromised skin grafts and flaps

Source	Summary of evidence	Conclusions
Saunders P, 2000 [10] Systematic review	Non-blind RCT, n = 48 patients found improved survival in HBOT group, particularly in participants aged >40.	No convincing evidence.
MSAC, 2000 [3]	Two poorly described trials.	Insufficient evidence, public funding not supported.
AHRQ, 2001 [6]	Refer to two RCTs, both with some limitations.	There is sufficient objective evidence that HBOT aids in wound healing.

Multiple sclerosis

Two health technology assessments and a systematic review recommend against the use of HBOT in this application.

Table 11: HBOT and MS

Source	Summary of evidence	Conclusions
Ball CM, 2002 [21] HTA (STEER)	Systematic review from 1993, no controlled studies since.	Found evidence of limited quality, which suggests that HBOT does not improve functional outcomes in people with multiple sclerosis.
MSAC, 2000 [3]	Drew on earlier review by NHS CRD.	Insufficient evidence, public funding not supported.
Bennett M, Heard R, 2001 [22] Systematic review	Included estimate of number needed to treat.	At this time, cannot recommend the routine treatment of MS with HBOT.

Cerebral palsy

The earlier position of MSAC that there was insufficient evidence is now supplemented by a recent RCT that found no benefit from HBOT in comparison with normal air. AETMIS considered that efficacy of HBOT in the treatment of cerebral palsy was still controversial [5].

Table 12: HBOT and cerebral palsy

Source	Summary of evidence	Conclusions
MSAC, 2000 [3]	No articles met selection criteria.	Insufficient evidence, public funding not supported.
Collet JP et al., 2001 [23] RCT [similar findings from this group in Hardy P et al., 2002 [24]]	Children with cerebral palsy aged 3-12 y randomly assigned HBOT (n=57) or slightly pressurised room air (n=54). All received 40 treatments over 2 months. For all outcomes, both groups improved over the course of the study, but without any difference between the two treatments.	HBOT did not improve the condition of children with cerebral palsy compared with slightly pressurised air. The improvement seen in both groups for all dimensions tested deserves further consideration.

Dental implants following radiotherapy

Table 13: HBOT and dental implants following radiotherapy

Source	Summary of evidence	Conclusions
Coulthard P et al., 2003 [25] Systematic review [Cochrane]	No RCTs identified.	Clinicians ought to make patients aware of the lack of reliable clinical evidence for or against the clinical effectiveness of HBOT in irradiated patients requiring dental implants.

Retinal artery occlusion

A recent HTA from the Wessex Institute considers that HBOT is an experimental treatment in this application.

Table 14: HBOT and retinal artery occlusion

Source	Summary of evidence	Conclusions
Patterson J, 2002 [26] HTA (STEER)	Two retrospective comparisons of case series. Found no reliable evidence about the effects of HBOT in retinal artery occlusion.	Until evidence from RCTs becomes available, HBOT remains an experimental treatment for central retinal artery occlusion.
Beiran I et al., 2001 [27] Retrospective comparison (see Patterson)	Mean visual acuity [VA] at discharge was 0.2981 (6/20) in the treated group and 0.1308 (6/46) in the control group ($p < 0.03$). Mean improvement in VA 0.1957 in HBOT group and 0.0457 in the controls ($p < 0.01$). Differences in outcome measures between treatment and control groups reflected the difference between treated and untreated hypertensive patients. No difference was found between treated and untreated non-hypertensive patients.	Early HBOT appears to have a beneficial effect on visual outcome. Further large-scale prospective controlled studies needed to confirm.
Fujii et al. , 1998 [28] Retrospective review over 8y	Reviewed 228 eyes, 38 treated with HBOT. In retinal artery occlusions, VA improved in 38% in the treated group and in 18% in the untreated group. In retinal vein occlusions, VA improved in 59% of eyes immediately after treatment but deteriorated later.	HBOT effective for retinal artery occlusions, not for retinal vein occlusions in this present series.

Other HBOT applications – HTA findings

The report by MSAC [3] referred to a number of other potential applications of HBOT where there was no more than weak evidence of benefit. In a number of cases no studies were found that met selection criteria for that HTA. Consequently, MSAC recommended that public funding should not be supported for HBOT in the following indications:

> decubitus ulcers, necrotising arachnidism, actinomycosis, cardiovascular conditions [including acute myocardial infarctions, cerebrovascular disease, and peripheral obstructive arterial disease], Bell's palsy, cluster and migraine headaches, Legg-Calve-Perthes disease (necrosis of the femoral head), sudden deafness and acoustic trauma, Crohn's disease, osteoporosis, cancer, cyanide poisoning, head trauma, cerebral oedema, acquired brain injury, cognitive impairment, senile dementia, glaucoma, keratoendotheliosis, HIV infection, anaemia from exceptional blood loss, insulin- dependent diabetes mellitus, facial neuritis, arthritis, spinal injuries and non-union of fractures.

Use of Transcutaneous Oxygen Measurements

The earlier AHFMR assessment noted advice received that use of TCO measurements allows prediction of which patients with wounds will heal if HBOT is used [1]. Patients with low pO_2 values in areas surrounding the wound are potential candidates for HBOT but are not treatable if pO_2 does not rise above specified values while breathing oxygen at a pressure of 2.5 atmospheres. For those eligible for HBOT, treatment should be discontinued if pO_2 does not rise within the first 14 days.

In preparing the present paper, only limited information was found on use of TCO in conjunction with HBOT. The assessment from AHRQ [6] made a number of statements:

- a case series from 1990 concluded that comparison of TCO levels in normal and hyperbaric oxygen is a reliable test to predict outcome in post traumatic limb ischemia;
- none of the studies used wound tissue hypoxia as a patient inclusion criterion [4];
- three studies of HBOT in diabetic wounds measured tissue oxygen levels round the wound but did not use this as an inclusion criterion for HBOT or for stratification in the analyses;
- studies by Wattel in 1989 and 1991 reported pO_2 measurement was a useful tool in predicting evolution and outcome of diabetic foot ulcers;
- there were conflicting results from 1996 studies on predictive value of measurements for chronic leg wounds;
- there is insufficient evidence from the studies examined by AHRQ to use tissue hypoxia as a criterion to determine whether adjunctive HBOT might be efficacious in reducing morbidity and mortality. None included information that was helpful for guiding treatment in individual patients;
- several studies assessed whether during HBOT were predictive of response. None of the studies stratified results by any other potential predictors of response; and
- it was not possible to determine which method of measuring tissue oxygen is the most reliable.

The impression is that the older studies might provide relatively limited evidence on the usefulness and reliability of TCO measurements. (Also, some of

the HBOT applications considered in the studies have not been supported by subsequent HTAs as having sufficient evidence of benefit.)

In the literature search for this paper, three publications were identified that measured the reliability of TCO measurements in the context of HBOT. These are summarized in the table. Such consideration of reliability is useful in helping to define the potential benefits of the measurements. The summaries of their findings are incomplete, reporting sensitivities and PPVs but not specificities.

Table 15: Reliability of transcutaneous oxygen measurements in HBOT

Source	Summary of evidence	Conclusions
Strauss MB et al., 2002 [29] Case series, both retrospective and prospective data	Recorded TCO measurements in room air and with hyperbaric oxygen in 190 patients with foot wounds; then looked at whether there was any effect on healing. TCO measurements under hyperbaric oxygen conditions defined a responder group (PtcO2 > 200 mmHg) with a sensitivity of 0.80 and a positive predictive value of 0.88 for healing, regardless of room air measurements when hyperbaric oxygen was used as an adjunct to wound management.	Information helps to objectify the indications for HBOT and predict healing especially in those patients with problem wounds of the foot and ankle.
Fife CE et al., 2002 [30] Retrospective analysis	N = 1,126 diabetics with lower extremity wounds, 75.6% improved after HBOT. Baseline sea-level air TCO identified degree of tissue hypoxia but had little relationship to outcome. Breathing oxygen at sea level unreliable for predicting failure, 68% reliable for predicting success after HBOT. The reliability of in-chamber TCO as an isolated measure was 74% with a positive predictive value of 58%. Combining information about sea-level air and in-chamber oxygen predicted failure of HBOT with a reliability of 75.8% and a positive predictive value of 73.3.	

Table 15: Reliability of transcutaneous oxygen measurements in HBOT (cont'd)

Source	Summary of evidence	Conclusions
Grolman RE et al., 2001 [31] Case series, comparing outcomes to TCO levels	N = 36 with critical limb ischemia and nonhealing ulcers. HBOT until healing occurred or failure was confirmed. All patients had a baseline TCO of <40 torr; 27 had an increase in TCO of >10 torr with oxygen inhalation at initial evaluation. Of these patients, 19 (70%) healed their wounds with HBOT. Increase in TCO <10 torr in 9 patients, and only one (11%) ultimately healed ($p < 0.01$).	Can predictably identify patients who are likely to benefit from HBOT using TCO at the time of initial evaluation.

Studies on TCO measurement in two other applications may be worth considering when assessing the reliability of this approach. Daviet et al. [32] evaluated reliability of TCO measurement in the upper limb, in the context of management of stroke patients. Using measurements on 18 normal volunteers they obtained TCO values on two separate occasions at one-day intervals. Reliability was poor with measurements of TCO varying by an average of 7.89 +/- 7.6 mmHg (coefficient of variation 96%) and was not sufficient to recommend this method in this indication.

De Graaf et al. [33] studied reproducibility of TCO and other types of measurement in 54 patients with various stages of peripheral vascular disease. These authors found that interobserver and intraobserver reproducibility for TCO was worse than other measures (intraclass correlation coefficient range 0.62-0.98, interobserver repeatability coefficient 30 mm Hg). They suggest that the repeatability coefficient be taken into account, especially when low values (or values around a cutoff value) are measured.

While TCO measurement appears to have been widely used in association with HBOT of wounds, there may be relatively limited information on its predictive value. Such information could be usefully obtained at individual HBOT facilities, reflecting local circumstances. In addition, the details on performance of TCO measurement given above suggest that those using this method should look critically at the reliability and robustness of such tests under local conditions. Such measurements may well be associated with significant error rates, which would need to be taken into account when making clinical decisions.

Other Applications of HBOT

Various other potential applications of HBOT have been addressed in the recent literature, typically in clinical studies of limited methodological rigour. Analysis of these is beyond the scope of this paper, but the topics considered may be of interest in pointing to potential future areas for assessment. They include treatment of radiation-induced brachial plexopathy (negative findings in an RCT); late sequelae of radiation following breast conserving surgery; tinnitus; calciphylaxis; radiation proctitis and cystitis in prostate cancer; combination treatment with photodynamic therapy; complications after macular hole surgery; and several from the list of additional, non-supported, applications identified by MSAC.

CONCLUSIONS

It is emphasized that, while this paper has identified some findings and opinions regarding HBOT, it is not a systematic review of the recent literature. However, even with this limited approach, some general comments can be made on the current status of HBOT from the perspective of assessment.

While there have been further studies since the AHFMR report on HBOT, the conclusions from systematic reviews and health technology assessments are generally similar to the earlier findings.

- There is support for use of HBOT for the following conditions:

  Decompression sickness, air and gas embolism, gas gangrene.

- There is conditional support for use of HBOT in:

  CO poisoning, osteoradionecrosis, diabetic wounds, necrotising soft tissue infections.

  (noting the still limited evidence of benefit and/or dependence on local protocols).

- There is no consensus on support for use of HBOT in:

  osteomyelitis, thermal burns, soft tissue radionecrosis, compromised skin grafts and flaps, dental implants following radiotherapy, retinal artery occlusion.

  (a tendency to recommend against use in these conditions, due to lack of evidence).

- Use of HBOT is not supported for:

  crush injury, non–diabetic wounds, multiple sclerosis, cerebral palsy.

  or for a large number of conditions identified in one of the health technology assessments:

  - decubitus ulcers, necrotising arachnidism, actinomycosis, cardiovascular conditions, Bell's palsy, cluster and migraine headaches, Legg-Calve-Perthes disease, sudden deafness and acoustic trauma, Crohn's disease, osteoporosis, cancer, cyanide poisoning, head trauma, cerebral oedema, acquired brain injury, cognitive impairment, senile dementia, glaucoma, keratoendotheliosis, HIV infection, anaemia from exceptional blood loss, insulin-dependent diabetes mellitus, facial neuritis, arthritis, spinal injuries and non-union of fractures.

- Information on the use of transcutaneous oxygen measurements in association with HBOT suggests that evidence of predictive value and analytical reliability may be limited and that local validation of these attributes by HBOT centres would be desirable.

A general theme in the systematic reviews and health technology assessments is the continuing lack of good quality evidence in support of most HBOT applications. Some publications have recognized the difficulties in undertaking good quality studies in some HBOT applications and have adjusted their recommendations accordingly. Others have been more insistent on the availability of randomized controlled trials. It has been pointed out that there is insufficient evidence to ascertain the appropriate time to initiate therapy in some applications and to establish criteria that determine whether patients will benefit [4].

There is likely to be a continuing tension between those who advocate the use of HBOT for management of various conditions, sometimes under circumstances of pressing clinical need, and those who require adequate proof of benefits in terms of health outcomes. Absence of proof of benefit is not the same as absence of benefit. On the other hand, assertions of the effectiveness of HBOT for a wide range of conditions in the absence of credible evidence are unconvincing and unhelpful. As noted in the AHFMR assessment, HBOT is a well established and useful health technology but there are a number of questions regarding the indications for which it is appropriate [2].

REFERENCES

1. Mitton C, Hailey D. *Hyperbaric oxygen treatment in Alberta.* Alberta Heritage Foundation for Medical Research, editor. Edmonton, AB: Health Technology Assessment; 1998. Report No. HTA8.
2. Mitton C, Hailey D. Health technology assessment and policy decisions on hyperbaric oxygen treatment. *Inter J Tech Assess in Health Care* 1999;15:661-70.
3. Medical Services Advisory Committee. *Hyperbaric oxygen therapy.* Medical Services Advisory Committee, editor. Canberra, AUS: Department of Health and Aged Care; November 2000.
4. Wang C, Schwaitzberg S, Berliner E, Zarin DA, Lau J. Hyperbaric oxygen for treatment wounds: a systematic review of the literature. *N Eng J Med* 2002;138(3):272-9.
5. Agence d'Evaluation des Technologies et des Modes i'Intervention en Sante (AETMIS). *[Hyperbaric oxygen therapy in Quebec].* Summary. Montreal, QC: AETMIS; 2000 [French].
6. Wang C, Lau J. Hyperbaric oxygen theapy in treatment of hypoxic wounds. Agency for Healthcare Research and Quality, November, 2001. Available: *http://cms.hhs.gov/coverage/download/8b3-mm2.pdf.*
7. Weaver LK, Hopkins RO, Chan KJ, Churchill S, Elliott CG, Clemmer TP, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Eng J Med* 2002;347(14):1057-67.
8. Dent THS. Hyperbaric oxygen therapy for carbon monoxide poisoning. In: Bazian Ltd. (ed). STEER: Succinct and Timely Evaluated Evidence Reviews2002:2(13). Wessex Institute for Health Research & Development, University of Southhampton. Available: *http://www.signpoststeer.org.*
9. Juurlink DN, Stanbrok MB, McGuigan MA, Juurlink DN, Stanbrook MB. Hyperbaric oxygen for carbon monoxide poisoning (Cochrane Review). In: *The Cochrane Library,* Issue 1 Oxford: Update Software 2003.
10. Saunders P. *Hyperbaric oxygen therapy in the management of carbon monoxide poisoning, osteoradionecrosis, burns, skin grafts and crush injury.* Birmingham: University of Birmingham, Department of Public Health and Epidemiology, editor; 2000.
11. Hampson NB, Zmaeff JL. Outcome of patients experiencing cardiac arrest with carbon monoxide poisoning treated with hyperbaric oxygen. *Ann Emerg Med* 2001;38(1):36-41.

12. Chou KJ, Fisher JL, Silver EJ. Characteristics and outcome of children with carbon monoxide poisoning with and without smoke exposure referred for hyperbaric oxygen therapy. *Pediatric Emergency Care* 2000;16(3):151-5.

13. Hawkins M. Severe carbon monoxide poisoning: outcome after hyperbaric oxygen therapy. *Brit J Anaesth* 2000;84(5):584-6.

14. Patterson J. Hyperbaric oxygen treatment for osteoradionecrosis. In: Bazian Ltd (ed). STEER: Succinct and Timely Evaluated Evidence Reviews 2002;2(16). Wessex Institute for Health Research & Development, University of Southhampton. Available: *http://www.signpoststeer.org.*

15. Maier A, Gaggl A, Klemen H, Santler G, Anegg U, Fell B, et al. Review of severe osteoradionecrosis treated by surgery alone or surgery with postoperative hyperbaric oxygenation. *Br J Oral Maxillofac Surg* 2000;38(3):173-6.

16. Kalani M, Jorneskog G, Naderi N, Lind F, Brismar K. Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers. Long-term follow-up. *J Diabetes Complications* 2002;16(2):153-8.

17. Mason J, O'Keeffe C, Hutchinson A, McIntosh A, Young R, Booth A. A systematic review of foot ulcer in patients with Type 1 diabetes mellitus II: treatment. *Diab Med* 1999;16(11):889-909.

18. Gawlik C, Schmacke N, Gibis B, Sander G, Rheinberger P. [Reimbursement and importance of hyperbaric oxygenation for diabetic foot ulcers in German publically funded ambulatory health care]. *Z Arztl Fortbild Qualitatssich* 2001;95(10):715-8 [German].

19. Landau Z, Schattner A. Topical hyperbaric oxygen and low energy laser therapy for chronic diabetic foot ulcers resistant to conventional treatment. *Yale J Biol Med* 2001;74(2):95-100.

20. Bissett AF. Hyperbaric oxygen therapy in people with necrotising fasciitis of Fournier's gangrene. In: Bazian Ltd (ed). STEER: Succinct and Timely Evaluated Evidence Reviews 2002;2(14). Wessex Institute for Health Research & Development, University of Southhampton. Available: *http://www.signpoststeer.org.*

21. Ball CM. Hyperbaric oxygen theapy for multiple sclerosis. In: Foxcroft DR, Muthu V (eds) STEER: Succinct and Timely Evaluated Evidence Reviews 2002:2(6). Available: *http://www.signpoststeer.org.*

22. Bennett M, Heard R. Treatment of multiple sclerosis with hyperbaric oxygen theapy. *Undersea Hyperb Med* 2001;28(2):117-22.

23. Collet JP, Vanasse M, Marois P, Amar M, Goldberg J, Lambert J, et al. Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial. *Lancet* 2001;357(9256):582-6.

24. Hardy P, Collet JP, Goldberg J, Ducruet T, Vanasse M, Lambert J, et al. Neuropsychological effects of hyperbaric oxygen therapy in cerebral palsy. *Dev Med Child Neurol* 2002;44(7):436-46.

25. Coulthard P, Esposito M, Worthington HV, Jokstad A. Therapeutic use of hyperbaric oxygen for irradiated dental implant patients: a systematic review. *J Dent Educ* 2003;67(1):64-8.

26. Patterson J. Hyperbaric oxygen therapy for central retinal artery occlusion. In: Bazian Ltd (ed). STEER: Succinct and Timely Evaluated Evidence Reviews 2002;2(16). Wessex Institute for Health Research & Development, University of Southampton. Available: *http://www.signpoststeer.org.*

27. Beiran I, Goldenberg I, Adir Y, Tamir A, Shupak A, Miller B. Early hyperbaric oxygen therapy for retinal artery occlusion. *Ophthalmol* 2001;11(4):345-50.

28. Fujii T, Joo J-H, Ibi K, Takahaski H, Akiya S, Konda I. Long term outcome of retinal artery or vein occlusion treated by hyperbaric oxygen. *Jap J Clin Ophthal 1998;*52(4):509-12.

29. Strauss MB, Bryant BJ, Hart GB. Transcutaneous oxygen measurements under hyperbaric oxygen conditions as a predictor for healing of problem wounds. *Foot Ankle Int* 2002;23(10):933-7.

30. Fife CE, Buyukcakir C, Otto GH, Sheffield PJ, Warriner III RA, Mader J. The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1144 patients. *Would Repair Regen* 2002;10(4):198-207.

31. Grolman RE, Wilkerson DK, Taylor J, Allinson P, Zatina MA. Transcutaneous oxygen measurements predict a beneficial response to hyperbaric oxygen theapy in patients with nonhealing wounds and critical limb ischemia. *Am Surg* 2001;67(11):1072-9.

32. Daviet JC, Rebeyrotte I, Lacroix P, Borie MJ, Verdie C, Dudognon P, et al. [Reliability of TcPO(2) measurement in the upper limb]. *Ann Readapt Med Phys* 2001;44(3):143-9 [French].

33. de Graaff JC, Ubbink DT, Legemate DA, de Haan RJ, Jacobs MJ. Interovserver and intraobserver reproducibility of peripheral blood and oxygen pressure measurements in the assessment of lower extremity arterial disease. *J Vasc Surg* 2001;33(5):1033-40.